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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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P.O. BOX 1022
MINNEAPOLIS, MN 55440-1022

EXAMINER	
GUSSOW, ANNE	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/550,934	TSUCHIYA ET AL.	
	Examiner	Art Unit	
	ANNE M. GUSSOW	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13* is/are pending in the application.

4a) Of the above claim(s) *4-6* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3 and 7-13* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *28 September 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☒ Other: *Appendix: sequence alignments*.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :5/25/06, 2/13/07, 5/18/07, 10/04/07, 2/12/08.

DETAILED ACTION

1. Applicant's election without traverse of Group I, claims 1-3 and 7-13, in the reply filed on April 16, 2008 is acknowledged.

2. Claims 4-6 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on April 16, 2008.

3. Claims 1-3, and 7-13 are under examination.

Information Disclosure Statement

4. The information disclosure statements (IDS) submitted on May 25, 2006, February 13, 2007, May 18, 2007, October 4, 2007, and February 12, 2008 have been considered by the examiner and an initialed copy of the IDS is included with the mailing of this Office Action.

Specification

5. The use of the trademark QIAexpress™ has been noted in this application. It should be capitalized wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

The trademark symbols and generic terminology have not been included for the trademarks in this application. Appropriate correction is required.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claim 3 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a minibody comprising 6 complementarity determining regions (CDRs), does not reasonably provide enablement for a minibody comprising a CDR or any combination less than 6, nor substitutions, insertions, deletions, or additions of just any amino acids. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 1 12, first paragraph, have been described by the court in In re Wands, 8 USPQ2d 1400 (CA FC 1988).

> Wands states on page 1404,
> "Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman.

> They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The claims are broadly drawn to a minibody comprising the amino acid sequences of a single CDR of SEQ ID Nos. 5, 7, 9, or 11. The claims are also broadly drawn to a minibody comprising substitutions, deletions, insertions or additions of amino acids.

The specification discloses production of a minibody that binds to CD22 from the variable regions of either of two known antibodies, LL2 or RFB4 (see example 1). The specification discloses specific PCR primers for amplification of the variable regions and cloning of the sequences into expression vectors to result in a diabody (see example 2). The specification does not disclose production of a minibody comprising a single CDR or fewer than 6 CDRs. The specification does not disclose just any substitutions, deletions, insertions, or additions of amino acids to the sequences of the known antibodies.

It is well established in the art that the formation of an intact antigen-binding site generally requires the association of the complete heavy and light chain variable regions of a given antibody, each of which consists of three CDRs which provide the majority of the contact residues for the binding of the antibody to its target epitope. The amino acid sequences and conformations of each of the heavy and light chain CDRs are critical in maintaining the antigen binding specificity and affinity which is characteristic of the parent immunoglobulin. It is expected that all of the heavy and light

chain CDRs in their proper order and in the context of framework sequences which maintain their required conformation, are required in order to produce a protein having antigen-binding function and that proper association of heavy and light chain variable regions is required in order to form functional antigen binding sites. Even minor changes in the amino acid sequences of the heavy and light variable regions, particularly in the CDRs, may dramatically affect antigen-binding function as evidenced by Rudikoff, et al. (Proceedings of the National Academy of Sciences, 1982. Vol. 79 page 1979). Rudikoff et al. teach that the alteration of a single amino acid in the CDR of a phosphocholine-binding myeloma protein resulted in the loss of antigen-binding function.

MacCallum, et al. (Journal of Molecular Biology, 1996. Vol. 262, pages 732-745) analyzed many different antibodies for interactions with antigen and state that although CDR3 of the heavy and light chain dominate, a number of residues outside the standard CDR definitions make antigen contacts (see page 733, right column) and non-contacting residues within the CDRs coincide with residues as important in defining canonical backbone conformations (see page 735, left column). Pascalis et al. (Journal of Immunology, 2002. Vol. 169, pages 3076-3084) demonstrate that grafting of the CDRs into a human framework was performed by grafting CDR residues and maintaining framework residues that were deemed essential for preserving the structural integrity of the antigen binding site (see page 3079, right column). Although abbreviated CDR residues were used in the constructs, some residues in all 6 CDRs were used for the constructs (see page 3080, left column).

The fact that not just one CDR is essential for antigen binding or maintaining the conformation of the antigen binding site is underscored by Casset et al. (Biochemical and Biophysical Research Communications, 2003. Vol. 307, pages 198-205) which constructed a peptide mimetic of an anti-CD4 monoclonal antibody binding site by rational design and the peptide was designed with 27 residues formed by residues from 5 CDRs (see entire document). Casset et al. also states that although CDR H3 is at the center of most if not all antigen interactions, clearly other CDRs play an important role in the recognition process (page 199, left column) and this is demonstrated in this work by using all CDRs except L2 and additionally using a framework residue located just before the H3 (see page 202, left column). Vajdos et al. (Journal of Molecular Biology, 2002. Vol. 320, pages 415-428) additionally state that antigen binding is primarily mediated by the CDRs more highly conserved framework segments which connect the CDRs are mainly involved in supporting the CDR loop conformations and in some cases framework residues also contact antigen (page 416, left column). Holm, et al. (Molecular Immunology, 2007. Vol. 44, pages 1075-1084) describes the mapping of an anti-cytokeratin antibody where although residues in the CDR3 of the heavy chain were involved in antigen binding unexpectedly a residue in CDR2 of the light chain was also involved (abstract). Chen, et al. (Journal of Molecular Biology, 1999. Vol. 293, pages 865-881) describe high affinity variant antibodies binding to VEGF wherein the results show that the antigen binding site is almost entirely composed of residues from heavy chain CDRs, CDR-H1, H2, H3 (page 866). Wu, et al. (Journal of Molecular Biology, 1999. Vol. 294, pages 151-162) state that it is difficult to predict which framework

residues serve a critical role in maintaining affinity and specificity due in part to the large conformational change in antibodies that accompany antigen binding (page 152 left column) but certain residues have been identified as important for maintaining conformation.

Regarding the substitution, insertion, deletion or addition of amino acids to the minibody sequences, Skolnick et al. (Trends in Biotechnology, 2000. Vol. 18 pages 34-39) teach that the skilled artisan is well aware that assigning functional activities for any particular protein or protein family based upon sequence homology is inaccurate, in part because of the multifunctional nature of proteins (e.g., Abstract and Sequence-based approaches to function prediction, page 34). Even in situations where there is some confidence of a similar overall structure between two proteins, only experimental research can confirm the artisan's best guess as to the function of the structurally related protein (see in particular Abstract and Box 2).

There is insufficient evidence or nexus that would lead the skilled artisan to produce functional minibody consisting of fewer than 6 CDRs. The specification does not teach how to produce an antibody or minibody with fewer than 6 CDRs.

In view of the lack of the predictability of the art to which the invention pertains, undue experimentation would be required to produce the claimed minibody with a reasonable expectation of success, absent a specific and detailed description in applicant's specification of how to effectively produce the claimed product and absent working examples providing evidence which is reasonably predictive that the claimed minibody would bind antigen, commensurate in scope with the claimed invention.

Claim Rejections - 35 USC § 102

8. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

9. Claims 1, 3, and 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Leung, et al. (WO 96/04925, published February 22, 1996, as cited on the IDS) as evidenced by the specification.

The claims recite a minibody that recognizes CD22. A minibody of any one of(a) to (f): (a) a minibody comprising the amino acid sequence of SEQ ID NO: 1 or 3; (b) a minibody functionally equivalent to the minibody of (a), and comprising the amino acid sequence of SEQ ID NO: 1 or 3 wherein one or more amino acids are substituted, inserted, deleted, and/or added; (c) a minibody comprising the amino acid sequences of a CDR of SEQ ID NOs: 5 and 7; (d) a minibody functionally equivalent to the minibody of (c), and comprising the amino acid sequence of a CDR of SEQ ID NOs: 5 and 7 wherein one or more amino acids are substituted, inserted, deleted, and/or added; (e) a minibody comprising the amino acid sequences of a CDR of SEQ ID NOs: 9 and 11; and (f) a minibody functionally equivalent to the minibody of (c), and comprising the amino acid sequence of a CDR of SEQ ID NOs: 9 and 11 wherein one or more amino acids are substituted, inserted, deleted, and/or added. An apoptosis-inducing agent comprising the minibody of claim 1 as an active ingredient. The apoptosis-inducing

agent of claim 7 that induces tumor cell apoptosis. The apoptosis-inducing agent of claim 8, wherein the tumor cell is a lymphoma or leukemic cell. An antitumor agent comprising the minibody of claim 1 as an active ingredient, wherein the tumor is a blood tumor.

Leung, et al. teach an antibody LL2 for the treatment of lymphoma or leukemia that binds to CD22. The sequence of the LL2 antibody is identical to the instant SEQ ID Nos. 5 and 7 (see sequence alignment). Leung, et al. teach an Fab' fragment of the LL2 antibody was used to treat lymphoma patients (see page 4). The instant specification discloses that a minibody comprises an antibody lacking a portion of a whole antibody that retains the ability to bind antigen. Since the claims do not define the specific sequence of the minibody and Leung, et al. teach fragments of an antibody with an identical sequence to SEQ ID Nos. 5 and 7 for the treatment of lymphoma (a blood cancer), all the limitations of the claims have been met.

10. Claims 1, 3, and 7-11 are rejected under 35 U.S.C. 102(b) as being anticipated by Fitzgerald, et al. (WO 98/41641, published September 24, 1998, as cited on the IDS) as evidenced by the specification.

The claims have been described supra.

Fitzgerald, et al. teach an antibody that binds to CD22 for inhibiting the growth of a malignant B-cell. Fitzgerald, et al. teach the sequence of the CD22 antibody is identical to the instant SEQ ID Nos. 9 and 11 (see sequence alignment). Fitzgerald, et al. teach an Fv fragment of the antibody. The instant specification discloses that a

minibody comprises an antibody lacking a portion of a whole antibody that retains the ability to bind antigen. Since the claims do not define the specific sequence of the minibody and Fitzgerald, et al. teach fragments of an antibody with an identical sequence to SEQ ID Nos. 9 and 11 for the treatment of malignant B-cells (a blood cancer), all the limitations of the claims have been met.

Claim Rejections - 35 USC § 103

11. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

12. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

13. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation

under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

14. Claims 1-3 and 7-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Leung, et al. (WO 96/04925, published February 22, 1996, as cited on the IDS) as evidenced by the specification in view of Hudson and Kortt (Journal of Immunological Methods, 1999. Vol. 231, pages 177-189, as cited on the IDS).

Claims 1, 3, and 7-11 have been described supra. Claims 2 and 12-13 recite wherein the minibody is a diabody.

Leung, et al. has been described supra. Leung, et al. teach a fragment of an antibody that binds to CD22. Leung, et al. do not teach a diabody. This deficiency is made up for in the teachings of Hudson and Kortt.

Hudson and Kortt teach construction of specific antibody fragments to form diabodies and triabodies that recognize antigen.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody fragments of Leung, et al and produce a diabody as taught by Hudson and Kortt.

One of ordinary skill in the art would have been motivated to and had a reasonable expectation of success to have used the antibody fragments of Leung, et al. and produce a diabody as taught by Hudson and Kortt because Hudson and Kortt teach

advantage to using bivalent diabody molecules for increased tumor penetration and faster clearance rates than full length antibodies, however a slower clearance rate than monomeric antibody fragments. Thus, it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the antibody fragments of Leung, et al. and produce a diabody in view of Hudson and Kortt.

Therefore, the invention as a whole was prima facie obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references.

Conclusion

15. No claims are allowed.

16. Any inquiry concerning this communication or earlier communications from the examiner should be directed to ANNE M. GUSSOW whose telephone number is (571)272-6047. The examiner can normally be reached on Monday - Friday 8:30 am - 5 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571) 272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only.

For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anne M. Gussow

May 30, 2008

/Larry R. Helms/
Supervisory Patent Examiner, Art Unit 1643